Unconjugated hyperbilirubinemia in term and late preterm infants: Screening

Authors: Ronald J Wong, BA, Vinod K Bhutani, MD, FAAP
Section Editor: Steven A Abrams, MD
Deputy Editor: Melanie S Kim, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Sep 2020. | **This topic last updated:** Jan 15, 2020.

INTRODUCTION

Almost all newborn infants develop a total serum or plasma bilirubin (TB) level greater than 1 mg/dL (17.1 micromol/L), which is the upper limit of normal for adults. As TB levels increase, neonatal jaundice can develop, noticeable as a visible yellowish discoloration of the skin and/or conjunctiva (as visualized on the sclerae) caused by bilirubin deposition. Term and late preterm infants (gestational age [GA] ≥35 weeks) with TB >25 mg/dL (428 micromol/L) or "severe" hyperbilirubinemia are at risk for developing bilirubin-induced neurologic dysfunction (BIND), which occurs when bilirubin crosses the blood-brain barrier and binds to brain tissue (figure 1). As a result, it is a standard of care to identify infants at risk for severe hyperbilirubinemia and to provide preventive therapy as needed. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Clinical manifestations'.)

The screening for neonatal unconjugated hyperbilirubinemia and identifying at-risk infants for severe hyperbilirubinemia are reviewed here. The clinical manifestations, prevention, and treatment of hyperbilirubinemia in term and late preterm infants are discussed separately. The pathogenesis and etiology of neonatal unconjugated hyperbilirubinemia and unconjugated hyperbilirubinemia in preterm infants (GA <35 weeks) are also discussed elsewhere. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations" and "Unconjugated hyperbilirubinemia in term and late preterm infants: Management" and "Unconjugated

hyperbilirubinemia in the newborn: Pathogenesis and etiology" and "Unconjugated hyperbilirubinemia in the preterm infant (less than 35 weeks gestation)".)

DEFINITIONS

Although there is no consensus amongst experts in the field in defining the clinical significance of varying total serum or plasma bilirubin (TB) levels for term and late preterm infants, the authors use the following definitions in this topic based on their experience.

- **Benign neonatal hyperbilirubinemia** is a transient and normal increase in bilirubin levels occurring in almost all newborn infants, which is also referred to as "physiologic jaundice."
- **Significant neonatal hyperbilirubinemia** in infants ≥35 weeks gestational age (GA) is defined as TB >95th percentile on the hour-specific Bhutani nomogram (figure 1) [1].
- **Severe neonatal hyperbilirubinemia** is defined as a TB >25 mg/dL (428 micromol/L). It is associated with an increased risk for developing bilirubin-induced neurologic dysfunction (BIND).
- **Extreme neonatal hyperbilirubinemia** is defined as a TB >30 mg/dL (513 micromol/L). It is associated with a significant increased risk for developing bilirubin-induced neurotoxicity and likelihood of kernicterus.
- **Bilirubin-induced neurologic dysfunction (BIND)** is due to brain damage from free bilirubin that crosses the blood-brain barrier and binds to brain tissue, as evidenced by both molecular and cytological injuries of brain cells. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Clinical manifestations'.)
    - **Acute bilirubin encephalopathy (ABE)** is used to describe the acute clinical manifestations of kernicterus. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Acute bilirubin encephalopathy'.)
    - **Chronic bilirubin encephalopathy (CBE)**, previously referred to as kernicterus, is used to describe the chronic and permanent post-icteric sequelae of extreme hyperbilirubinemia. (See "Unconjugated hyperbilirubinemia in term and late

preterm infants: Epidemiology and clinical manifestations", section on 'Chronic bilirubin encephalopathy (kernicterus)'.)

CONSEQUENCES OF HYPERBILIRUBINEMIA

Bilirubin-induced neurologic dysfunction — Observational data in neonates have reported the major complication of an elevated total serum or plasma bilirubin (TB) level (hyperbilirubinemia) is a spectrum of bilirubin-associated neurotoxicity known as bilirubin-induced neurologic dysfunction (BIND). BIND occurs when unconjugated bilirubin, which is not bound to albumin (also referred to as "free" or "unbound bilirubin" or UB), crosses the blood-brain barrier, enters the brain, and causes brain injury (figure 2). BIND is an array of neurologic findings [2,3] manifested as disorders in visuocortical pathways [4], sensorineural hearing [5], proprioception (leading to gait abnormalities) [6], speech, and language [7]. Chronic bilirubin encephalopathy (CBE), previously referred to as kernicterus, is the progressive and extreme chronic form of BIND associated with permanent neurologic sequelae, such as choreo-athetoid cerebral palsy, upward gaze abnormalities, enamel dysplasia of deciduous teeth, and sensorineural impairment [1]. Deafness may occur as an isolated event.

Two advances in medical care in the late 1960s have impacted on the way in which hyperbilirubinemia is managed and altered the associated morbidity and mortality. They include the widespread use of Rh(D) immunoglobulin to Rh-negative mothers, which dramatically decreased the incidence of Rh-isoimmune neonatal hemolytic disease, and the introduction of phototherapy, which significantly reduced the need for exchange transfusions and the risk of developing severe hyperbilirubinemia. Thus, the risk of CBE was reduced from its peak in the 1950s through the 1970s. Nevertheless, isolated cases of CBE, a mostly preventable condition, continue to be reported despite the implementation of major society guidelines [8-13]. In particular, infants with hemolytic disease (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency) are at-risk for severe hyperbilirubinemia and kernicterus [1,13-15]. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Bilirubin-induced neurologic injury'.)

Prevalence of kernicterus — The following is an estimated risk for kernicterus for screening TB levels using population-based data from developed countries (eg, high-income countries) [16-18]:

- TB >20 and ≤25 mg/dL (342 and 428 micromol/L) – Risk of kernicterus is rare.

- TB >25 and ≤30 mg/dL (428 and 513 micromol/L) – 6 percent
- TB >30 and ≤35 mg/dL (513 and 599 micromol/L) – 14 to 25 percent
- TB >35 mg/dL (599 micromol/L) – Almost all infants will have signs of kernicterus

SCREENING FOR HYPERBILIRUBINEMIA

Goals — The goal for predischarge screening is to identify at-risk neonates and prevent mortality and morbidity during infancy of adverse outcomes of severe hyperbilirubinemia. When neonates are screened, monitored, and treated appropriately and in a timely manner, almost all infants with hyperbilirubinemia, even those with risk factors (table 1), will have benign outcomes and avoid the adverse effects of bilirubin-induced neurologic dysfunction (BIND). (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Risk factors'.)

Components — In our center, screening consists of:

- Clinical assessment of all infants for the physical presence of jaundice and additional hyperbilirubinemia risk factors (table 1). (See 'Clinical assessment' below.)
- Universal measurement of bilirubin consistent with the updated 2009 American Academy of Pediatrics (AAP) guidelines as the physical presence of jaundice alone is a suboptimal screening tool [19]. In our center, screening is done by measuring total serum or plasma bilirubin (TB) levels. Infants with TB values ≥95th percentile are at-risk for developing severe hyperbilirubinemia and possibly BIND if not treated in a timely manner [20,21]. Alternatively, transcutaneous bilirubin (TcB) screening is used at other centers. (See 'Bilirubin testing' below and 'Choice of bilirubin test for screening' below.)
- Appropriate follow-up based upon risk assessment and the infant's age at the time of discharge that identifies progression of hyperbilirubinemia during the first week of life. (See 'Follow-up' below.)

Our approach — Our approach to prevent the development of severe hyperbilirubinemia is to identify and treat at-risk infants using a structured systematic approach that combines a predischarge TB for all infants (ie, universal screening), clinical risk assessment (table 1), and follow-up based on individual clinical parameters [19]. In our practice, universal bilirubin screening measuring TB is performed at the time of routine metabolic screening in all infants prior to discharge. Our screening approach is consistent with the AAP and the United Kingdom's National Institute of Health and Clinical Excellence

(NICE guidelines) clinical practice guidelines to identify, evaluate, and treat term and late preterm infants (gestational age [GA] >35 weeks) at risk for developing severe hyperbilirubinemia [1,19]. Instituting this type of systematic screening decreases the risk of severe hyperbilirubinemia [19,20,22,23]. (See 'Choice of bilirubin test for screening' below and 'Recommended universal screening' below and "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Risk factors'.)

A large prospective multicenter study center that used universal screening and implemented the 2004 AAP guidelines reported that combining a predischarge TB or TcB measurement with clinical risk factors (earlier GA, bruising, positive direct antiglobulin test, Asian race, exclusive breastfeeding, blood type incompatibility, and the extent of jaundice) was more predictive of the use of subsequent phototherapy compared with TB/TcB or risk factors alone [22].

Infants with TB values ≥95th percentile are at-risk for developing severe hyperbilirubinemia and possibly bilirubin-induced neurologic dysfunction (BIND) if not treated in a timely manner. For these at-risk infants, additional evaluation to determine the underlying etiology, subsequent monitoring of TB levels, and possibly therapy to prevent or treat severe hyperbilirubinemia are provided (algorithm 1). Infants who require intervention to either prevent or treat hyperbilirubinemia can be identified using the newborn hyperbilirubinemia assessment calculator (calculator 1). (See 'Additional evaluation' below and "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Clinical manifestations' and "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Criteria for intervention based on risk severity assessment'.)

For infants who do not meet the requirements for intervention, the results of the assessment help in nutritional and lactational management, discharge planning and scheduling of the initial follow-up appointment. The timing of follow-up appointments depends on age at discharge and whether risk factors for hyperbilirubinemia are present. If appropriate follow-up cannot be arranged, we delay discharge until the infant is greater than 72 hours of age, the period of greatest risk for neonatal hyperbilirubinemia. At the follow-up appointment, the need for follow-up TB measurement is based on the infant's appearance and the interval history (eg, jaundice progression, hydration status, adequacy of intake, and weight relative to his/her discharge weight to guide lactation management). (See 'Follow-up' below.)

The need for readmission is based on the probability of developing a TB that meets the

threshold for initiating phototherapy based on the TB and the presence or absence of additional risk factors. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Assessment of risk severity'.)

Clinical assessment — Clinical assessment consists of routine evaluation of the newborn for the onset and progression of jaundice while in the hospital and determining if there are risk factors for severe hyperbilirubinemia in addition to an elevated bilirubin measurement (table 1) [24,25].

Onset and progression of jaundice — All term and late preterm infants should be routinely assessed for the onset and progression of jaundice every 8 to 12 hours while in the hospital as part of the routine newborn management (see "Overview of the routine management of the healthy newborn infant"). Bilirubin measurement should be performed in the following settings when jaundice is detected. However, because visual assessment is not a reliable indicator of severe hyperbilirubinemia, a low threshold for measuring bilirubin is appropriate [24,25]. Bilirubin measurement should be performed for:

- Any infant who develops jaundice before 24 hours of age.
- Any infant >24 hours of age when jaundice appears to be excessive for age (eg, jaundice below the level of the umbilicus).
- Failure of jaundice resolution after seven days of age in a formula-fed infant or 14 to 21 days in a breastfed infant [26].
- Infants who are still jaundiced at age two weeks must have a measurement of direct or conjugated bilirubin.

Risk assessment — Prior to discharge, every infant should be assessed for the risk of developing subsequent severe hyperbilirubinemia (table 1). As noted above, the combination of risk assessment and universal bilirubin screening provides the most accurate prediction of severe hyperbilirubinemia (TB >20 mg/dL [342 micromol/L]) (table 1). (See 'Our approach' above and "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Risk factors'.)

In addition to an elevated TB level, major risk factors include:

- GA 35 to 36 weeks
- Exclusive breastfeeding associated with suboptimal intake
- Hemolytic disease

- Significant bruising (eg, cephalohematoma from birth trauma)
- Sibling who received phototherapy
- East Asian race

Bilirubin testing — A measurement of bilirubin in infants before discharge helps to identify those who are at risk for developing severe hyperbilirubinemia. In our center, all infants are tested (universal screening), whereas in other institutions selective screening is performed based on clinical findings of jaundice and identification of additional risk factors for hyperbilirubinemia.

Bilirubin screening can be performed by TB or TcB measurements. TB and TcB values are compared with age-specific percentile nomograms based on age of the neonate to determine whether the infant has hyperbilirubinemia (and the severity) or is at-risk for developing severe hyperbilirubinemia. (See 'Choice of bilirubin test for screening' below.)

Recommended universal screening — Universal bilirubin screening before discharge has been recommended by an expert panel of neonatologists and pediatricians, including the authors, to identify infants at high risk for developing severe hyperbilirubinemia based on large cohort observational studies showing that universal screening has reduced the incidence of severe hyperbilirubinemia [1,8,27-29]. An alternative approach to universal bilirubin testing is selective screening, in which the need for bilirubin testing is based on clinical judgement on the presence of jaundice and/or clinical risk factors (table 1). However, we recommend universal screening consistent with the AAP guidelines as there is good evidence that universal screening compared with selective screening reduces the risk of severe hyperbilirubinemia. In our center, universal bilirubin screening measuring TB is performed at the time of routine metabolic screening in all infants prior to discharge.

Acceptance of universal screening for hyperbilirubinemia, however, has been limited because of concerns about the cost and the need for additional blood sampling [30]. In some institutions, TcB measurements are used to screen all term and late preterm infants prior to discharge, because it decreases the need for phlebotomy, reduces laboratory costs, and appears to be as effective as TB as a screening tool in detecting severe hyperbilirubinemia [27,31-33]. Although TcB can be used as a screening tool for infants of all ethnicities, it is not a substitute for a TB measurement, especially when therapeutic interventions are being considered. (See 'Transcutaneous bilirubin (TcB)' below.)

Nevertheless, observational data from large cohorts comparing universal versus selective risk assessment strategies to screen for neonatal hyperbilirubinemia found universal

screening was superior in reducing the risk of severe hyperbilirubinemia as follows:

- In a large retrospective study of late preterm and term infants, the incidence of hyperbilirubinemia exceeding the AAP threshold recommended for exchange transfusion was lower in birth facilities that had implemented universal screening compared with facilities without universal screening (0.17 versus 0.45 percent) [27].

- In a large multicenter study, both the incidence of severe (TB >20 mg/dL, 342 micromol/L) and extreme (TB >25 mg/dL, 428 micromol/L) decreased after the implementation of universal screening compared with pre-implementation historical controls [34]. In addition, the rate of hospital readmissions for neonatal jaundice decreased after implementation of universal screening.

The US Preventive Services Task Force in 2009, the Advisory Committee on Heritable Disorders in Newborns and Children in 2012, and the American Academy of Family Physicians in 2014, have concluded that there is insufficient evidence that universal screening is warranted, as there is a lack of direct evidence demonstrating that screening reduces kernicterus [35-37]. However, given the challenges for selective screening, we as well as other experts in the field continue to advocate for universal screening based on the data demonstrating a link between severe hyperbilirubinemia and progressive severity of BIND [38,39].

Follow-up — Regardless of whether universal or selective bilirubin screening is performed, appropriate follow-up after discharge is essential, particularly with the discharge of infants before 48 hours of life as TB levels have rarely reached their peak by this age (see 'Timing' below and "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Peak TB levels and time to resolution'). At the time of discharge, follow-up is arranged, information and written guidelines about jaundice are provided to the parents, and instructions are given to the family on when and whom to contact for medical issues (eg, jaundice and adequacy of feeding) prior to their appointment [1].

At the follow-up appointment, the infant's weight and percent change from birth weight, adequacy of intake, pattern of voiding and transition of stool color, and the presence or absence of jaundice are assessed [1,19,40]. The need for further bilirubin measurement is based on the infant's appearance, the interval medical history (weight change and intake), presence of hyperbilirubinemia risk factors, especially GA, and the predischarge bilirubin level.

TB levels at the low-risk zone do not completely eliminate the potential for developing significant hyperbilirubinemia. This was illustrated in an Israeli study of 25,439 neonates in which 0.6 percent of the cohort was readmitted for hyperbilirubinemia (mean TB = 18.7 mg/dL [320 micromol/L]) [41]. Of these 143 patients, 6 had predischarge TB in the low-risk zone and 46 in the intermediate-low-risk zone. These results demonstrate the importance of timely follow-up after discharge even for infants who were identified as low-risk for clinically significant hyperbilirubinemia during birth hospitalization.

Even in follow-up after discharge, clinicians should remain mindful of the hyperbilirubinemia risk factors, because unrecognized G6PD deficiency, inherited causes of red blood cell disorders, and lack of screening for UGT polymorphisms may contribute to persistent or recurrent unconjugated hyperbilirubinemia at postnatal age >7 days.

Timing — The timing of the follow-up appointment depends on the age of the patient at discharge and whether major risk factors for hyperbilirubinemia are present. TB concentrations typically peak between 72 and 96 hours of age in Caucasian and African-American infants and later in others (eg, Asian and preterm infants) [42,43]. Infants who are discharged prior to the anticipated peak TB require follow-up during this peak period to assess for jaundice and decide whether a bilirubin measurement is needed. Infants who are discharged prior to 72 hours should be seen within two days of discharge. In general, earlier follow-up is required for infants born before 38 weeks gestation and/or have additional risk factors for severe hyperbilirubinemia (table 1) [19].

The following is our approach for appropriate follow-up based on the nomogram percentile of initial screening TB level (figure 1), GA, and whether additional risk factors are present (table 1) [19]:

- **Infants 35 to 37 weeks GA with additional risk factors:**
  - Screening TB >95th percentile − Remain in the hospital and follow-up TB measurement in four to eight hours.
  - Screening TB between 75th and 95th percentile − Remain in the hospital and follow-up TB measurement in 4 to 24 hours.
  - Screening TB <75th percentile − Potential discharge. If discharged before 72 hours of life, mandatory follow-up visit within 48 hours of discharge with measurement of TB.
- **Infants 35 to 37 weeks GA and no additional risk factors:**

- Screening TB >95th percentile − Remain in the hospital and follow-up TB measurement in 4 to 24 hours.
- Screening TB between 75th and 95th percentile − Remain in the hospital and follow-up TB measurement within 24 hours.
- Screening TB <75th percentile − Potential discharge. If discharged before 72 hours of life, mandatory follow-up visit within 48 hours of discharge with measurement of TB.

- **Infants >38 weeks GA with additional risk factors:**
  - Screening TB >95th percentile − Remain in the hospital and follow-up TB measurement in 4 to 24 hours.
  - Screening TB between 75th and 95th percentile − Remain in the hospital and follow-up TB measurement within 24 hours.
  - Screening TB <75th percentile − Potential discharge. If discharged before 72 hours of life, mandatory follow-up visit within 48 hours of discharge with measurement of TB.
- **Infants >38 weeks GA and no additional risk factors:**
  - Screening TB >95th percentile − Remain in the hospital and follow-up TB measurement in 4 to 24 hours.
  - Screening TB between 75th and 95th percentile − Remain in the hospital and follow-up TB measurement within 24 hours.
  - Screening TB <75th percentile − Potential discharge. If discharged before 72 hours of life, follow-up visit within 48 hours of discharge and assessment at visit determines the need for further TB measurement. Additional TB testing is indicated if there is a history of inadequate intake (eg, few wet diapers) or poor feeding, ongoing weight loss, or the appearance of jaundice on physical examination.

Determining the need for and arranging follow-up is particularly challenging when infants are discharged just prior to a weekend. Under these circumstances, clinicians should use their clinical judgment. Earlier follow-up is required for infants with multiple risk factors or who are born late preterm. As examples, if on Thursday or Friday when discharging a

formula-fed infant with a GA of 41 weeks without additional risk factors including no evidence of jaundice (table 1), it is acceptable to schedule that infant for a follow-up visit on the following Monday or Tuesday. On the other hand, if a breastfed infant with multiple risk factors (eg, predischarge TB in the high-intermediate zone or higher, primiparous mother, GA of <38 weeks, and exclusively breastfed) is being discharged, that infant must be seen within two days of discharge or sooner (regardless of weekends or holidays). The reasons for the follow-up decision should be documented in the chart [19].

If appropriate follow-up cannot be arranged, discharge should be delayed until follow-up can be ensured or the period of greatest risk for hyperbilirubinemia has passed (72 to 96 hours of age). (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations", section on 'Risk factors'.)

CHOICE OF BILIRUBIN TEST FOR SCREENING

Overview — The gold standard for neonatal bilirubin testing is measuring total serum or plasma bilirubin (TB). However, transcutaneous bilirubin (TcB) is a reasonable alternative because it decreases the need for phlebotomy, reduces laboratory costs, and appears to be as effective as TB as a screening tool in detecting the risk of developing severe hyperbilirubinemia [27,31-33].

TB and TcB values are compared with age-specific percentile-based nomograms (figure 1) [8,31]. TcB values >75th percentile on the Bhutani nomogram or >95th percentile on a transcutaneous nomogram need to be confirmed by TB measurements, as higher TcB values often underestimate TB (see 'Limitations of TcB' below). In our center, we obtain TB in all infants at the time of the newborn screening for metabolic disorders, thus obviating the need for an additional blood sample but not the additional cost involved with this test.

Total serum or plasma bilirubin (TB) — TB is plotted on an age-specific, percentile-based nomogram developed from a racially diverse population of newborn infants born in Philadelphia, referred to as the Bhutani nomogram (figure 1) [8]. In this group of infants with a 60 percent rate of breastfeeding, 95th percentile values for TB for term and late preterm infants were determined as follows [8]:

- 8 mg/dL (137 micromol/L) at 24 hours of age
- 11 mg/dL (188 micromol/L) at 36 hours of age
- 13 mg/dL (222 micromol/L) at 48 hours of age
- 16 mg/dL (274 micromol/L) at 72 hours of age

Infants with hour-specific TB values ≥95th percentile are at increased risk for developing severe hyperbilirubinemia. Phototherapy is initiated to prevent development of severe hyperbilirubinemia and the need for an exchange transfusion. The risk for severe hyperbilirubinemia and the threshold for intervention based upon the hour-specific TB value may be determined using the newborn hyperbilirubinemia assessment calculator (calculator 1). (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Assessment of risk severity'.)

In patients with TB >95th percentile, a subsequent TB measurement is needed to direct clinical care. Additional evaluation may determine an underlying pathologic cause that may be amenable to treatment or require earlier intervention. (See 'Additional evaluation' below and "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology".)

Epidemiology — Neonatal TB values vary substantially among institutions because of differences in racial composition, hemolytic conditions, or breastfeeding practices. This was illustrated in a multinational study of nine centers located in four countries that compared TB values of newborn infants. TB values at 30 hours of age were plotted on the Bhutani nomogram [8]. The proportion of infants (≥35 weeks gestation) with TB ≥95th percentile at 30 hours of age varied as follows [44]:

- 5 and 8 percent from two centers in Hong Kong, China
- 8 and 21 percent from two centers in Jerusalem, Israel
- 39 percent from a center in Kobe, Japan
- Results varied among four centers in the United States: 6 percent (Cleveland, OH), 9 percent (Providence, RI), 10 percent (Stanford, CA), and 16 percent (Philadelphia, PA)

These results demonstrate that clinicians need to be aware of the prevalence of hyperbilirubinemia in their given population. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Causes of significant unconjugated neonatal hyperbilirubinemia'.)

Methods to measure bilirubin — Two main methods are used to measure TB. In our center, the screening TB is measured by a chemical laboratory analyzer using the diazo method.

- **Chemical laboratory analyzers**–- These analyzers used in core laboratories directly measure TB concentrations in whole blood, serum, or plasma samples via a chemical

reaction (diazo method) or spectrophotometrically. Core laboratory bilirubin measurements provide a gold standard for bilirubin determination and are used, in general, to evaluate other methods of bilirubin measurement. The age-specific percentile-based nomogram in general clinical use and used in the American Academy of Pediatrics (AAP) practice guideline is based upon TB measurements performed by chemical laboratory analyzers utilizing the diazo method [8]. These analyzers require a blood sample of approximately 0.3 mL, larger than what is required for spectrophotometric methods, but still obtainable via a heelstick.

High interlaboratory and inter-instrument variabilities in TB measurements have been reported [45,46]. It is important that laboratories perform routine quality assurance and proficiency testing, as changes, including recalibration of bilirubin assays, can result in significant clinical effects. This was illustrated by a study demonstrating the effects of a recalibration of a commercially available assay that resulted in reductions of birth hospital phototherapy and readmissions for phototherapy [47].

- **Nonchemical photometric devices** – These devices, which are predominantly used at the point-of-care, measure bilirubin concentrations spectrophotometrically and require minimal blood volumes (eg, capillary sample by heelstick). Many of these devices are also blood gas analyzers, and thus several analyses (eg, pH, PaO_2, and levels of sodium and calcium) may be measured on a single sample.

Measurements utilizing nonchemical photometric devices correlate with the standard set by the chemical laboratory analyzers but these devices are less accurate when TB is elevated. At TB levels >14.6 mg/dL (250 micromol/L) [48,49], these devices may underestimate the TB, and values at these bilirubin concentrations should be confirmed with standard core laboratory methods [48]. In circumstances when TB is approaching or exceeds the 95th percentile, therapy should be initiated while awaiting confirmatory results from the core chemical laboratory.

Transcutaneous bilirubin (TcB) — TcB devices use multiwavelength spectral reflectance from the skin surface and can be used to estimate TB and thus avoid blood sampling. For a specific percentile and hour of life, the levels of bilirubin in the nomogram extrapolated from TcB measurements are generally lower than those of the TB nomogram [30]. As a result, TcB values that exceed the 75th percentile or values >12.5 mg/dL (214 micromol/L) need to be confirmed by measuring TB.

TcB nomograms have been developed across different ethnic groups and regions of the world [31,50-60]. In several reports of racially and ethnically diverse groups of term and

late preterm newborns, close correlations between TcB and TB measurements have been demonstrated [33,61,62]. However, systematic reviews have shown TcB nomogram values vary among different ethnic groups [51,63]. Although genetic differences may explain the variation in TcB nomograms, differences in study designs (eg, enrollment criteria, equipment, and frequency of other risk factors [breastfeeding versus formula-feeding]) also may have contributed to the differences in the results. There are also significant variations among different instruments [64,65]. When TcB is used clinically as a substitute for TB, values of new instruments should always be compared with TB measurements performed by the laboratory to ensure good correlation [19].

Benefits — The use of TcB screening reduces the number of blood tests for bilirubin determinations for infants with visible jaundice without compromising detection of infants with significant TB values (eg, >75th percentile) [66-70]. In addition, the implementation of TcB in a hospital- and community-screening setting was associated with a reduction in the incidence of severe TB and readmission for phototherapy, and lower duration and rate of phototherapy improved screening and reduced cost [68,70].

Limitations of TcB — In the following settings, TcB measurements may not accurately reflect TB levels. If there is any question regarding the validity of TcB measurements, TB should be obtained.

- TcB measurements are not reliable in infants undergoing phototherapy and should not be used in during phototherapy [1,71].
- TcB accuracy is reduced with prior exposure of the infant to sunlight or phototherapy.
- TcB can underestimate TB, but can be used 24 hours after discontinuation of phototherapy.
- TcB testing may be affected by skin pigmentation [32,33,65,72,73]. TcB overestimates TB in infants who are dark-skinned [65,73,74], and might underestimate TB in light-skinned infants [73].
- High TB levels – At high levels of TB (>15 mg/dL [257 micromol/L]), TcB measurements underestimate TB and need to be confirmed by standard laboratory methods [48,75-77]. Still, TcB can replace TB in most circumstances when TB is <15 mg/dL (257 micromol/L) [1,48].

When to confirm with TB — If TcB is used for screening, a confirmatory TB should be measured in the following settings [19,78,79]:

- When TcB exceeds the 75th percentile on the TB nomogram for phototherapy (figure 1)
- If the TcB is within 3 mg/dL of the phototherapy threshold levels
- At follow-up after discharge, if the TcB is >12.5 mg/dL (214 micromol/L)

When therapeutic intervention is being considered (phototherapy or exchange transfusion), therapy should be initiated while awaiting confirmatory results.

Outpatient setting — There are limited data regarding TcB's reliability and accuracy in identifying at-risk infants after birth hospitalization. As a result, before TcB outpatient measurements can be recommended for routine care, further studies are required to determine its efficacy and to optimize standardized protocols for its use.

- In one study of 120 infants (mean age of 90.4 hours), there was good correlation between TcB and TB (r = 0.78) [80]. Although TcB values were lower than TB, TcB <12 mg/dL (205 micromol/L) always reliably predicted that the TB was <15 mg/dL (257 micromol/L). TcB values between 13 and 14 mg/dL (222 to 239 micromol/L) similarly predicted a TB <17 mg/dL (291 micromol/L). The authors concluded that the use of TcB in the outpatient setting was a safe and reliable screen for assessing hyperbilirubinemia in infants recently discharged.

- In another study of 87 paired measurements of TcB and TB of term infants ≤8 days of age, mean TcB levels were greater than mean TB (15.1 versus 13.6 mg/dL [258 versus 233 micromol/L]) [81]. In comparison with inpatient measurements, there was greater variability between TcB and TB with outpatient measurements. In this study, the sensitivity of TcB to detect outpatient infants at risk for developing hyperbilirubinemia was 87 percent and the specificity was 58 percent. In contrast to the above study, the authors concluded that further studies are needed to determine the efficacy of outpatient TcB screening.

Other concerns regarding the use of TcB measurements in the outpatient setting is the initial cost of equipment, personnel time for training and performing the test, and the standardization of testing, such as body location for testing. For example, TcB measurements performed on the forehead in an infant who may have been exposed to direct sunlight may not be as reliable as an alternate unexposed site, such as the sternum.

ADDITIONAL EVALUATION

Subsequent TB testing and TB rate of rise — Infants who have total serum or plasma

bilirubin (TB) values ≥95th percentile or suspicion of hemolytic disease require subsequent measurement(s) of TB and further evaluation to determine the etiology of jaundice. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology".)

TB should be repeated in 4 to 24 hours depending upon the infant's age, TB value, and anticipated rate of TB rise. The 95th percentile of the TB nomogram rises at a rate of 0.2 mg/dL per hour between 0 and 72 hours of life. TB increases at rates ≥0.2 mg/dL/hour are usually indicative of the presence of hemolysis reflecting an increase in bilirubin production, which overwhelms an infant's ability to sufficiently eliminate bilirubin and increases the risk of severe hyperbilirubinemia.

Additional tests — Additional testing is typically only needed for infants who meet the criteria for phototherapy. These additional tests include the following [1]. For infants with other risk factors for developing severe hyperbilirubinemia, such as earlier gestational age (35 to 37 weeks), further diagnostic work-up and treatment may be initiated for lower TB concentrations (table 1):

- **Blood type and direct or indirect antiglobulin test (Coombs)** – The mother's blood type usually should be known from prenatal testing and can be compared with the infant's blood type to see if there is a possibility of isoimmune hemolytic disease. For neonates with incompatibility of blood types with the mother, antibody-mediated hemolysis can be confirmed by a positive direct or indirect antiglobulin tests. (See "Postnatal diagnosis and management of hemolytic disease of the fetus and newborn", section on 'Types of HDFN'.)

- **Complete blood count and smear** – A low hemoglobin may be indicative of hemolysis, which can be confirmed by presence of fragmented cells in the blood smear. (See "Approach to the child with anemia", section on 'Laboratory evaluation'.)

- **Reticulocyte count** – A rising reticulocyte count during the first 72 hours of life is consistent with red blood cell destruction (eg, hemolysis), but not proven for the first week after birth.

- **Glucose-6-phosphate dehydrogenase (G6PD) measurement** – If either parent is of African, Mediterranean or East Asian ancestry, or if the TB concentration is ≥18 mg/dL (308 micromol/L), G6PD should be measured. Because the turnaround time for G6PD results might not be soon enough to affect clinical decisions, clinicians taking care of infants with multicultural heritage should obtain a careful history of the ethnic/geographic background of the family to better appreciate the risk of G6PD

deficiency. If there is any clinical concern, it is prudent to provide parental education regarding avoidance of agents that trigger hemolysis until laboratory results are available [82]. Parents must also be counseled at the time of birth hospital discharge regarding the possibility of a rapid and dramatic increase in the infant's TB level and be advised to bring the infant to the hospital immediately should there be an increase in the degree of visible jaundice or any evidence of poor feeding, lethargy, or an abnormal cry.

- **End-tidal CO, corrected for ambient CO, concentration (ETCOc)** – Because the breakdown of heme results in the production of equimolar quantities of bilirubin and carbon monoxide (CO), ETCOc, provides a noninvasive assessment of bilirubin production [83-87]. Elevated ETCOc values (>1.7 ppm) can identify infants with increased bilirubin production due to increased red blood cell breakdown (eg, hemolysis), who may require additional evaluation, therapy, or close monitoring [88]. As a result, we use ETCOc to aid us in confirming active hemolysis in neonates in our center. A commercial ETCOc instrument is now available and has been evaluated at a number of institutions [89,90].

- Evaluation for conjugated (direct) hyperbilirubinemia – Infants with cholestasis may also present with jaundice and elevated TB levels. They can be distinguished from those infants with physiologic hyperbilirubinemia as they typically have elevated conjugated or direct-reacting bilirubin levels. If the conjugated bilirubin is >0.5 mg/dL or the direct bilirubin is >1 mg/dL (17.1 micromol/L), the possibility of sepsis should be considered and subsequent management should include obtaining blood cultures and administering empiric antibiotics with follow-up measurement of TB [91]. If the TB level remains elevated over the next two to three days, the infant should be evaluated for causes of cholestasis, including biliary atresia. (See "Approach to evaluation of cholestasis in neonates and young infants" and "Management and outcome of sepsis in term and late preterm infants".)

Other tests that may not be universally available but may be helpful in management decisions include unbound bilirubin and bilirubin binding capacity:

- **Unbound bilirubin** – Unbound (or "free") bilirubin (UB) is more likely to cross the blood-brain barrier and cause brain injury. However, in newborns without hyperbilirubinemia, most bilirubin is normally bound to albumin, resulting in low levels of UB. In patients with TB concentrations >20 mg/dL, the capacity of albumin to bind bilirubin might be exceeded, leading to higher levels of UB, increasing the risk of bilirubin-induced neurologic dysfunction (BIND). Although measurement of UB

concentration may be a more sensitive and specific indicator of BIND [92,93], it is **not** clinically available in North America and is only used in a research setting.

- **Bilirubin/albumin (B/A) ratio** – The ratio of bilirubin to albumin (B/A) in conjunction with measurements of TB can serve as an approximate surrogate for UB to determine whether therapeutic interventions (eg, exchange transfusion) should be initiated (figure 3) [1,94-96]. In term neonates, a B/A molar ratio >7 to 8 (bilirubin mg/dL to albumin g/dL) might indicate that all bilirubin binding sites on albumin are occupied. Any further increase in bilirubin would be associated with exponentially increasing levels of UB, which can cross the blood-barrier result in a higher (unmeasured) risk of neurotoxicity [97]. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Assessment of risk severity'.)

  Preterm and sick infants often have decreased serum albumin concentrations and a reduced binding capacity, resulting in a higher proportion of UB for a given TB compared with healthy term infants [95]. As a result, in these patients, a lower B/A ratio and lower TB thresholds are used to initiate therapy [1]. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Assessment of risk severity'.)

  Other factors that may reduce albumin binding and thus increase the risk of BIND include:

  - Drugs such as sulfisoxazole, moxalactam, and ceftriaxone
  - Acidosis
  - Hypercarbia

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Neonatal jaundice".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have

about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Jaundice in babies (The Basics)")
- Beyond the Basics topics (see "Patient education: Jaundice in newborn infants (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Total serum or plasma bilirubin (TB) >1 mg/dL (17.1 micromol/L) occurs in almost all newborn infants. Infants with severe hyperbilirubinemia (TB >25 mg/dL [428 micromol/L]) are at risk for developing bilirubin-induced neurologic dysfunction (BIND), presenting acutely as acute bilirubin encephalopathy (ABE) and, if not adequately addressed, long-term neurologic sequelae referred to as chronic bilirubin encephalopathy (CBE), previously known as kernicterus. (See 'Definitions' above.)
- Although the incidence of CBE is low, cases continue to occur. Contributing, potentially correctable factors include early hospital discharge of newborn infants (≤48 hours of age) without adequate follow-up and failure to recognize and evaluate the severity of hyperbilirubinemia. (See 'Consequences of hyperbilirubinemia' above.)
- In order to identify and treat infants at risk for developing severe hyperbilirubinemia, we use a systematic approach for all newborns based on a combination of universal screening of a predischarge TB, clinical risk assessment (table 1), and follow-up based on individual clinical parameters. (See 'Screening for hyperbilirubinemia' above.)
- TB and transcutaneous bilirubin (TcB) measurements can both be used to measure and monitor bilirubin levels. Although TcB is generally a reliable and less invasive screening test, it may not accurately reflect TB in infants who are dark- (overestimation) or light-skinned (underestimation), with higher bilirubin concentrations (TcB measurements underestimate TB), or in those who are

undergoing or have recently discontinued phototherapy. TcB can be used 24 hours after the discontinuation of phototherapy. As a result, TcB needs to be confirmed by measuring TB in patients with high TB, prior to initiation of a therapeutic intervention, or when more accurate measurement of bilirubin is needed to make a management decision. (See 'Total serum or plasma bilirubin (TB)' above and 'Transcutaneous bilirubin (TcB)' above.)

- Infants with TB >95th percentile for age are at increased risk for developing severe hyperbilirubinemia. The risk for developing severe hyperbilirubinemia and the threshold for intervention based upon the hour-specific bilirubin value, the presence of additional risk factors, and the gestational age may be determined using the newborn hyperbilirubinemia assessment calculator (calculator 1). (See 'Clinical assessment' above and "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Criteria for intervention based on risk severity assessment'.)

- Infants with TB ≥95th percentile or suspicion of hemolytic disease require subsequent measurement(s) of TB and further evaluation to determine the etiology of jaundice. (See 'Additional evaluation' above.)

- Prior to discharge, risk assessment for severe hyperbilirubinemia should be performed, which (along with the age of the patient at discharge) guides the timing of the initial follow-up appointment. (See 'Risk assessment' above and 'Follow-up' above.)

- At the time of discharge, appropriate follow-up is arranged, information and written guidelines about jaundice are provided to the parents, and instructions for when to contact medical staff are given to the family. Timing of follow-up appointments depends on age at discharge and whether risk factors for hyperbilirubinemia are present. If appropriate follow-up cannot be arranged, discharge is delayed until the infants is greater than 72 hours of age, the period of greatest risk for neonatal hyperbilirubinemia. (See 'Follow-up' above.)

- At the follow-up appointment, the infant's weight and percent change from birth weight, adequacy of intake, pattern of voiding and stooling, and the presence or absence of jaundice are assessed. Clinical judgment based upon the infant's appearance and the interval medical history is used to determine the need for a TB measurement. (See 'Follow-up' above.)

REFERENCES

1. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114:297.
2. Bhutani VK, Wong R. Bilirubin-induced neurologic dysfunction (BIND). Semin Fetal Neonatal Med 2015; 20:1.
3. Johnson L, Bhutani VK. The clinical syndrome of bilirubin-induced neurologic dysfunction. Semin Perinatol 2011; 35:101.
4. Good WV, Hou C. Visuocortical bilirubin-induced neurological dysfunction. Semin Fetal Neonatal Med 2015; 20:37.
5. Olds C, Oghalai JS. Audiologic impairment associated with bilirubin-induced neurologic damage. Semin Fetal Neonatal Med 2015; 20:42.
6. Rose J, Vassar R. Movement disorders due to bilirubin toxicity. Semin Fetal Neonatal Med 2015; 20:20.
7. Wusthoff CJ, Loe IM. Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. Semin Fetal Neonatal Med 2015; 20:52.
8. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999; 103:6.
9. Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breast-fed term newborns. Pediatrics 1995; 96:730.
10. AAP Subcommittee on Neonatal Hyperbilirubinemia. Neonatal jaundice and kernicterus. Pediatrics 2001; 108:763.
11. Mah JK, Wirrell E. All is not well: the continual challenges of bilirubin encephalopathy. Can J Neurol Sci 2005; 32:273.
12. Christensen RD, Lambert DK, Henry E, et al. Unexplained extreme hyperbilirubinemia among neonates in a multihospital healthcare system. Blood Cells Mol Dis 2013;

50:105.

13. Bhutani VK, Johnson LH, Jeffrey Maisels M, et al. Kernicterus: epidemiological strategies for its prevention through systems-based approaches. J Perinatol 2004; 24:650.

14. Watchko JF, Kaplan M, Stark AR, et al. Should we screen newborns for glucose-6-phosphate dehydrogenase deficiency in the United States? J Perinatol 2013; 33:499.

15. Nock ML, Johnson EM, Krugman RR, et al. Implementation and analysis of a pilot in-hospital newborn screening program for glucose-6-phosphate dehydrogenase deficiency in the United States. J Perinatol 2011; 31:112.

16. Bhutani VK, Johnson L. Kernicterus in the 21st century: frequently asked questions. J Perinatol 2009; 29 Suppl 1:S20.

17. Alkén J, Håkansson S, Ekéus C, et al. Rates of Extreme Neonatal Hyperbilirubinemia and Kernicterus in Children and Adherence to National Guidelines for Screening, Diagnosis, and Treatment in Sweden. JAMA Netw Open 2019; 2:e190858.

18. Bhutani VK, Zipursky A, Blencowe H, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res 2013; 74 Suppl 1:86.

19. Maisels MJ, Bhutani VK, Bogen D, et al. Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. Pediatrics 2009; 124:1193.

20. Newman TB, Liljestrand P, Escobar GJ. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. Arch Pediatr Adolesc Med 2005; 159:113.

21. Gonçalves A, Costa S, Lopes A, et al. Prospective validation of a novel strategy for assessing risk of significant hyperbilirubinemia. Pediatrics 2011; 127:e126.

22. Bhutani VK, Stark AR, Lazzeroni LC, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr 2013; 162:477.

23. Keren R, Luan X, Friedman S, et al. A comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and near-term infants. Pediatrics 2008; 121:e170.

24. Riskin A, Tamir A, Kugelman A, et al. Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? J Pediatr 2008; 152:782.

25. Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. Arch Dis Child Fetal Neonatal Ed 2009; 94:F317.

26. Maisels MJ, Clune S, Coleman K, et al. The natural history of jaundice in predominantly breastfed infants. Pediatrics 2014; 134:e340.

27. Kuzniewicz MW, Escobar GJ, Newman TB. Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. Pediatrics 2009; 124:1031.

28. Mah MP, Clark SL, Akhigbe E, et al. Reduction of severe hyperbilirubinemia after institution of predischarge bilirubin screening. Pediatrics 2010; 125:e1143.

29. Darling EK, Ramsay T, Sprague AE, et al. Universal bilirubin screening and health care utilization. Pediatrics 2014; 134:e1017.

30. Suresh GK, Clark RE. Cost-effectiveness of strategies that are intended to prevent kernicterus in newborn infants. Pediatrics 2004; 114:917.

31. Maisels MJ, Kring E. Transcutaneous bilirubin levels in the first 96 hours in a normal newborn population of > or = 35 weeks' gestation. Pediatrics 2006; 117:1169.

32. Maisels MJ, Kring E. Transcutaneous bilirubinometry decreases the need for serum bilirubin measurements and saves money. Pediatrics 1997; 99:599.

33. Bhutani VK, Gourley GR, Adler S, et al. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. Pediatrics 2000; 106:E17.

34. Eggert LD, Wiedmeier SE, Wilson J, Christensen RD. The effect of instituting a prehospital-discharge newborn bilirubin screening program in an 18-hospital health system. Pediatrics 2006; 117:e855.

35. US Preventive Services Task Force. Screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy: US Preventive Services Task Force recommendation statement. Pediatrics 2009; 124:1172.

36. Health Services and Resources Administration Federal Advisory Committees. Previou sly nominated conditions table: conditions added to the Recommended Uniform Scr

eening Panel (RUSP) by the Secretary. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/previous-nominations.html (Accessed on January 09, 2020).

37. Muchowski KE. Evaluation and treatment of neonatal hyperbilirubinemia. Am Fam Physician 2014; 89:873.

38. Newman TB, Kemper AR. Avoiding Harm From Hyperbilirubinemia Screening. JAMA Pediatr 2019.

39. Watchko JF, Maisels MJ. Avoiding Harm From Hyperbilirubinemia Screening. JAMA Pediatr 2019.

40. Maisels MJ, Coffey MP, Gendelman B, et al. Diagnosing Jaundice by Eye-Outpatient Assessment of Conjunctival Icterus in the Newborn. J Pediatr 2016; 172:212.

41. Bromiker R, Bin-Nun A, Schimmel MS, et al. Neonatal hyperbilirubinemia in the low-intermediate-risk category on the bilirubin nomogram. Pediatrics 2012; 130:e470.

42. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med 2001; 344:581.

43. Maisels MJ. What's in a name? Physiologic and pathologic jaundice: the conundrum of defining normal bilirubin levels in the newborn. Pediatrics 2006; 118:805.

44. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. J Perinatol 2001; 21 Suppl 1:S63.

45. Vreman HJ, Verter J, Oh W, et al. Interlaboratory variability of bilirubin measurements. Clin Chem 1996; 42:869.

46. Lo SF, Doumas BT, Ashwood ER. Performance of bilirubin determinations in US laboratories--revisited. Clin Chem 2004; 50:190.

47. Kuzniewicz MW, Greene DN, Walsh EM, et al. Association Between Laboratory Calibration of a Serum Bilirubin Assay, Neonatal Bilirubin Levels, and Phototherapy Use. JAMA Pediatr 2016; 170:557.

48. Grohmann K, Roser M, Rolinski B, et al. Bilirubin measurement for neonates: comparison of 9 frequently used methods. Pediatrics 2006; 117:1174.

49. Barko HA, Jackson GL, Engle WD. Evaluation of a point-of-care direct spectrophotometric method for measurement of total serum bilirubin in term and

near-term neonates. J Perinatol 2006; 26:100.

50. Varvarigou A, Fouzas S, Skylogianni E, et al. Transcutaneous bilirubin nomogram for prediction of significant neonatal hyperbilirubinemia. Pediatrics 2009; 124:1052.

51. Kaplan M, Bromiker R. Variation in Transcutaneous Bilirubin Nomograms across Population Groups. J Pediatr 2019; 208:273.

52. De Luca D, Romagnoli C, Tiberi E, et al. Skin bilirubin nomogram for the first 96 h of life in a European normal healthy newborn population, obtained with multiwavelength transcutaneous bilirubinometry. Acta Paediatr 2008; 97:146.

53. Engle WD, Lai S, Ahmad N, et al. An hour-specific nomogram for transcutaneous bilirubin values in term and late preterm Hispanic neonates. Am J Perinatol 2009; 26:425.

54. Sanpavat S, Nuchprayoon I, Smathakanee C, Hansuebsai R. Nomogram for prediction of the risk of neonatal hyperbilirubinemia, using transcutaneous bilirubin. J Med Assoc Thai 2005; 88:1187.

55. Bental YA, Shiff Y, Dorsht N, et al. Bhutani-based nomograms for the prediction of significant hyperbilirubinaemia using transcutaneous measurements of bilirubin. Acta Paediatr 2009; 98:1902.

56. Fouzas S, Mantagou L, Skylogianni E, et al. Transcutaneous bilirubin levels for the first 120 postnatal hours in healthy neonates. Pediatrics 2010; 125:e52.

57. Yu ZB, Dong XY, Han SP, et al. Transcutaneous bilirubin nomogram for predicting neonatal hyperbilirubinemia in healthy term and late-preterm Chinese infants. Eur J Pediatr 2011; 170:185.

58. Akahira-Azuma M, Yonemoto N, Mori R, et al. An hour-specific transcutaneous bilirubin nomogram for Mongolian neonates. Eur J Pediatr 2015; 174:1299.

59. Han S, Yu Z, Liu L, et al. A Model for Predicting Significant Hyperbilirubinemia in Neonates From China. Pediatrics 2015; 136:e896.

60. Bromiker R, Goldberg A, Kaplan M. Israel transcutaneous bilirubin nomogram predicts significant hyperbilirubinemia. J Perinatol 2017; 37:1315.

61. Slusher TM, Angyo IA, Bode-Thomas F, et al. Transcutaneous bilirubin measurements and serum total bilirubin levels in indigenous African infants. Pediatrics 2004;

113:1636.

62. Fine KL, Carey WA, Schuster JAW, et al. Defining the limitations of transcutaneous bilirubin measurement in late preterm newborns. J Perinatol 2017; 37:658.

63. De Luca D, Jackson GL, Tridente A, et al. Transcutaneous bilirubin nomograms: a systematic review of population differences and analysis of bilirubin kinetics. Arch Pediatr Adolesc Med 2009; 163:1054.

64. Ebbesen F, Vandborg PK, Trydal T. Comparison of the transcutaneous bilirubinometers BiliCheck and Minolta JM-103 in preterm neonates. Acta Paediatr 2012; 101:1128.

65. Taylor JA, Burgos AE, Flaherman V, et al. Discrepancies between transcutaneous and serum bilirubin measurements. Pediatrics 2015; 135:224.

66. Kaplan M, Shchors I, Algur N, et al. Visual screening versus transcutaneous bilirubinometry for predischarge jaundice assessment. Acta Paediatr 2008; 97:759.

67. Mishra S, Chawla D, Agarwal R, et al. Transcutaneous bilirubinometry reduces the need for blood sampling in neonates with visible jaundice. Acta Paediatr 2009; 98:1916.

68. Wainer S, Parmar SM, Allegro D, et al. Impact of a transcutaneous bilirubinometry program on resource utilization and severe hyperbilirubinemia. Pediatrics 2012; 129:77.

69. van den Esker-Jonker B, den Boer L, Pepping RM, Bekhof J. Transcutaneous Bilirubinometry in Jaundiced Neonates: A Randomized Controlled Trial. Pediatrics 2016; 138.

70. McClean S, Baerg K, Smith-Fehr J, Szafron M. Cost savings with transcutaneous screening versus total serum bilirubin measurement for newborn jaundice in hospital and community settings: a cost-minimization analysis. CMAJ Open 2018; 6:E285.

71. Casnocha Lucanova L, Matasova K, Zibolen M, Krcho P. Accuracy of transcutaneous bilirubin measurement in newborns after phototherapy. J Perinatol 2016; 36:858.

72. Wainer S, Rabi Y, Parmar SM, et al. Impact of skin tone on the performance of a transcutaneous jaundice meter. Acta Paediatr 2009; 98:1909.

73. Samiee-Zafarghandy S, Feberova J, Williams K, et al. Influence of skin colour on diagnostic accuracy of the jaundice meter JM 103 in newborns. Arch Dis Child Fetal Neonatal Ed 2014; 99:F480.

74. Olusanya BO, Imosemi DO, Emokpae AA. Differences Between Transcutaneous and Serum Bilirubin Measurements in Black African Neonates. Pediatrics 2016; 138.

75. Engle WD, Jackson GL, Sendelbach D, et al. Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinemia in a primarily Hispanic population. Pediatrics 2002; 110:61.

76. Schumacher RE. Transcutaneous bilirubinometry and diagnostic tests: "the right job for the tool". Pediatrics 2002; 110:407.

77. Engle WD, Jackson GL, Stehel EK, et al. Evaluation of a transcutaneous jaundice meter following hospital discharge in term and near-term neonates. J Perinatol 2005; 25:486.

78. Maisels MJ. Use TcB as a screening tool for jaundiced newborns. AAP News 2004; 25:9.

79. Taylor JA, Burgos AE, Flaherman V, et al. Utility of Decision Rules for Transcutaneous Bilirubin Measurements. Pediatrics 2016; 137.

80. Maisels MJ, Engle WD, Wainer S, et al. Transcutaneous bilirubin levels in an outpatient and office population. J Perinatol 2011; 31:621.

81. Wickremasinghe AC, Karon BS, Cook WJ. Accuracy of neonatal transcutaneous bilirubin measurement in the outpatient setting. Clin Pediatr (Phila) 2011; 50:1144.

82. Kaplan M, Hammerman C, Bhutani VK. Parental education and the WHO neonatal G-6-PD screening program: a quarter century later. J Perinatol 2015; 35:779.

83. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics 2001; 108:31.

84. Stevenson DK, Vreman HJ. Carbon monoxide and bilirubin production in neonates. Pediatrics 1997; 100:252.

85. Bartoletti AL, Stevenson DK, Ostrander CR, Johnson JD. Pulmonary excretion of carbon monoxide in the human infant as an index of bilirubin production. I. Effects of gestational and postnatal age and some common neonatal abnormalities. J

Pediatr 1979; 94:952.

86. Vreman HJ, Stevenson DK, Oh W, et al. Semiportable electrochemical instrument for determining carbon monoxide in breath. Clin Chem 1994; 40:1927.

87. Stevenson DK, Vreman HJ, Oh W, et al. Bilirubin production in healthy term infants as measured by carbon monoxide in breath. Clin Chem 1994; 40:1934.

88. Bhutani VK, Srinivas S, Castillo Cuadrado ME, et al. Identification of neonatal haemolysis: an approach to predischarge management of neonatal hyperbilirubinemia. Acta Paediatr 2016; 105:e189.

89. Castillo Cuadrado ME, Bhutani VK, Aby JL, et al. Evaluation of a new end-tidal carbon monoxide monitor from the bench to the bedside. Acta Paediatr 2015; 104:e279.

90. Christensen RD, Lambert DK, Henry E, et al. End-tidal carbon monoxide as an indicator of the hemolytic rate. Blood Cells Mol Dis 2015; 54:292.

91. Davis AR, Rosenthal P, Escobar GJ, Newman TB. Interpreting conjugated bilirubin levels in newborns. J Pediatr 2011; 158:562.

92. Amin SB, Wang H, Laroia N, Orlando M. Unbound Bilirubin and Auditory Neuropathy Spectrum Disorder in Late Preterm and Term Infants with Severe Jaundice. J Pediatr 2016; 173:84.

93. Wennberg RP, Ahlfors CE. A different view on bilirubin binding. Pediatrics 2006; 118:846.

94. Ahlfors CE. Criteria for exchange transfusion in jaundiced newborns. Pediatrics 1994; 93:488.

95. Cashore WJ. Free bilirubin concentrations and bilirubin-binding affinity in term and preterm infants. J Pediatr 1980; 96:521.

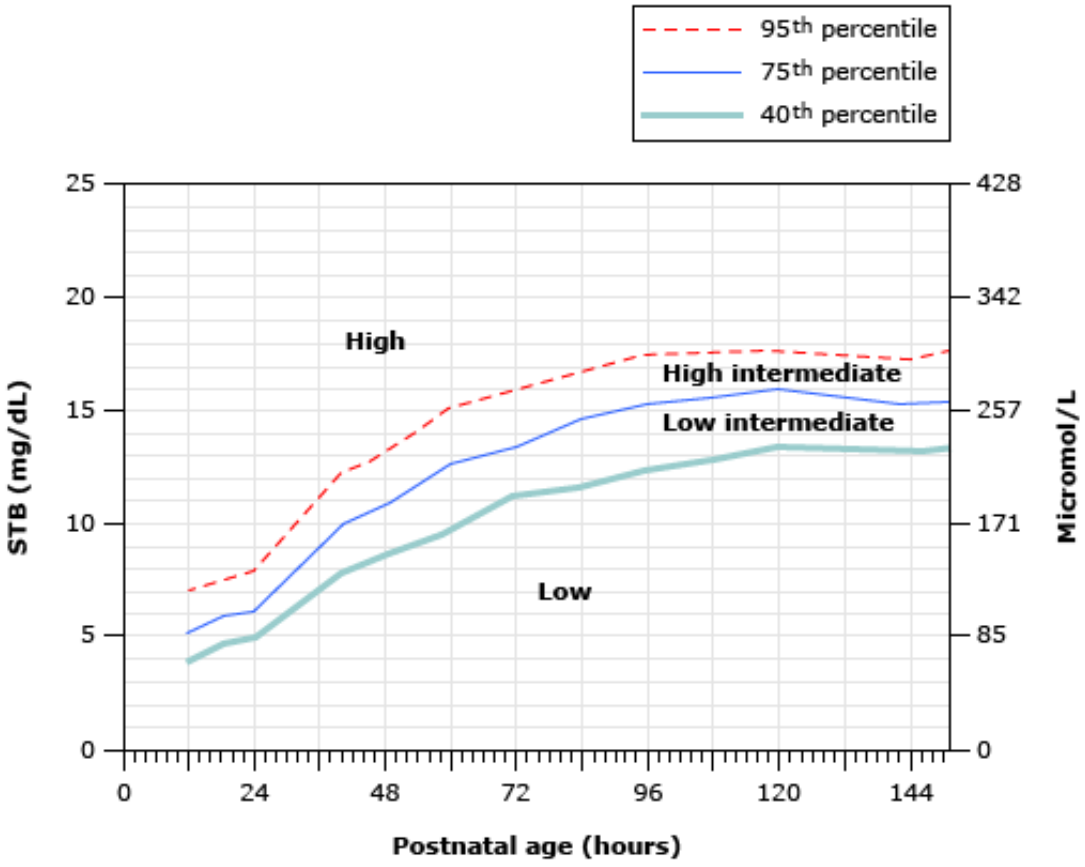
96. Iskander I, Gamaleldin R, El Houchi S, et al. Serum bilirubin and bilirubin/albumin ratio as predictors of bilirubin encephalopathy. Pediatrics 2014; 134:e1330.

97. Ahlfors CE, Wennberg RP, Ostrow JD, Tiribelli C. Unbound (free) bilirubin: improving the paradigm for evaluating neonatal jaundice. Clin Chem 2009; 55:1288.

Topic 5008 Version 54.0

GRAPHICS

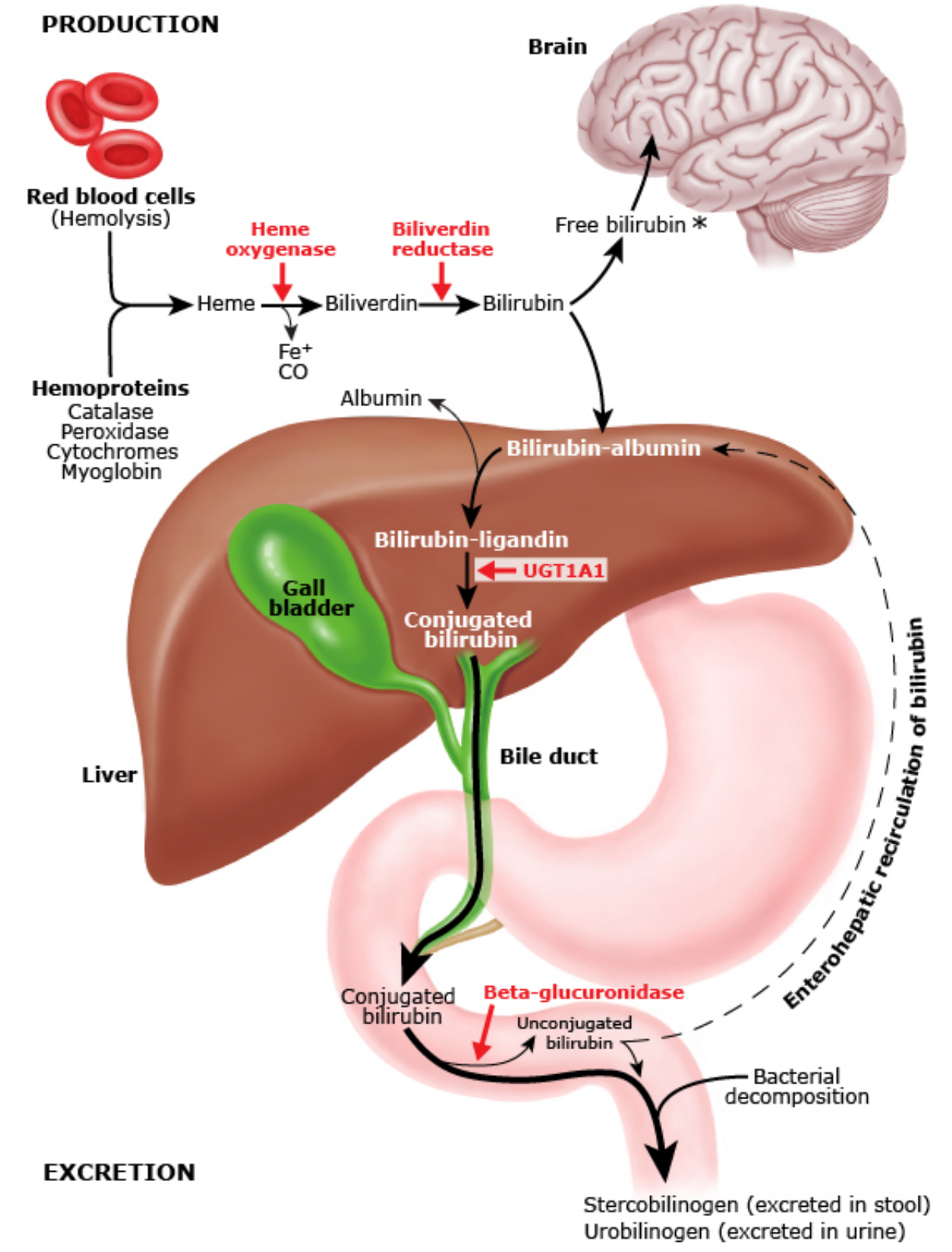
Nomogram of hour-specific serum or plasma total bilirubin (TB) concentration in healthy term and near-term newborns



Risk zones are designated according to percentile: high (TB ≥95th), high intermediate (95th >TB ≥75th), low intermediate (75th >TB ≥40th), and low (TB <40th). Infants with values in the high risk zone are at increased risk for the development of clinically significant hyperbilirubinemia requiring intervention.

Graphic 70863 Version 17.0

Bilirubin production, metabolism, and excretion



Schematic diagram demonstrating the production, metabolism, and excretion of bilirubin.

*Physiologic mechanisms that reduce the movement of free bilirubin across the blood-brain barrier include binding to plasma albumin and rapid uptake, conjugation, and clearance by the liver. These protective mechanisms are less efficient in neonates (especially preterm infants) and individuals with inherited disorders of bilirubin conjugation. As a result, these patients are at risk for bilirubin-induced neurotoxicity.

Adapted from: Hansen TWR, Bratlid D. Physiology of neonatal unconjugated hyperbilirubinemia. In: Care of the Jaundiced Neonate, Stevenson DK, Maisels MJ, Watchko JF (Eds), McGraw-Hill Companies, New York 2012.

Graphic 121543 Version 4.0

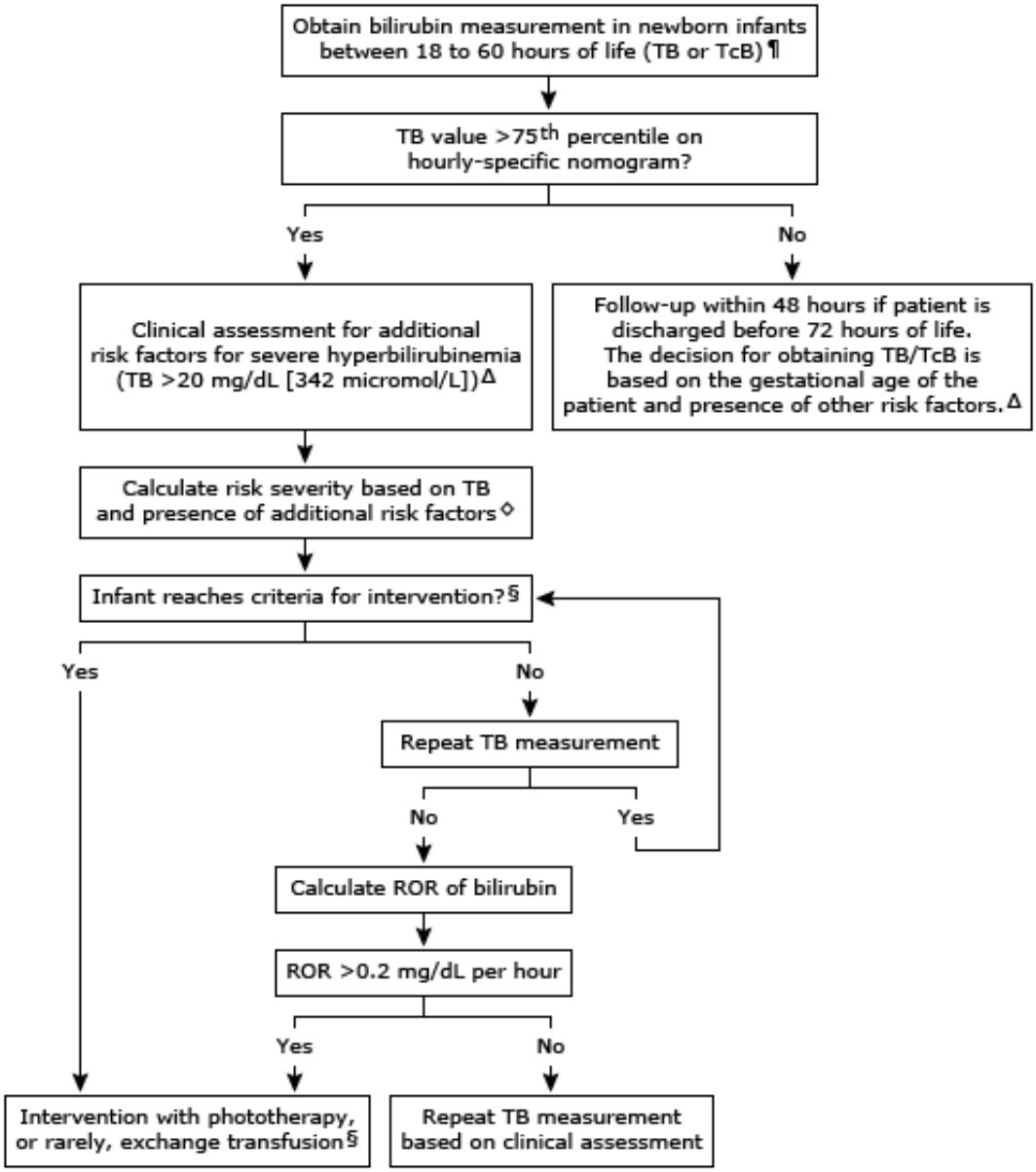
Risk factors for development of severe hyperbilirubinemia in infants of 35 or more weeks gestation (in approximate order of importance)

Major risk factors
Predischarge TB or TcB level in the high-risk zone
Jaundice observed in the first 24 hours
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCOc
Gestational age 35 to 36 weeks
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race*
Minor risk factors
Predischarge TB or TcB level in the high intermediate-risk zone
Gestational age 37 to 38 weeks
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥25 years
Male gender
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TB or TcB level in the low-risk zone
Gestational age ≥41 weeks
Exclusive bottle feeding
Black race*
Discharge from hospital after 72 hours

TB: total serum or plasma bilirubin; TcB: transcutaneous bilirubin; G6PD: glucose-6-phosphate dehydrogenase; ETCOc: end-tidal carbon monoxide concentration.
* Race as defined by mother's description.

Graphic 64584 Version 21.0

Universal screening and management of unconjugated hyperbilirubinemia in asymptomatic term and late preterm neonates (gestational age >35 weeks)*



This algorithm is based on the clinical practice of universal bilirubin screening for term and late preterm provided by the authors of the UpToDate content on the screening and management of unconjugated hyperbilirubinemia in term and late preterm infants.

TB: total plasma/serum bilirubin; TcB: transcutaneous bilirubin; ROR: rate of rise.

* Exchange transfusion is indicated for any symptomatic infant due to bilirubin-induced neurotoxicity. While setting up for the exchange transfusion, intensive phototherapy is initiated.

¶ TB and TcB values are plotted on the age-specific (hourly), percentile-based Bhutani nomogram. A confirmatory TB value is obtained when TcB measurement exceeds the 95th percentile on the TcB nomogram or 75th percentile on the TB nomogram.

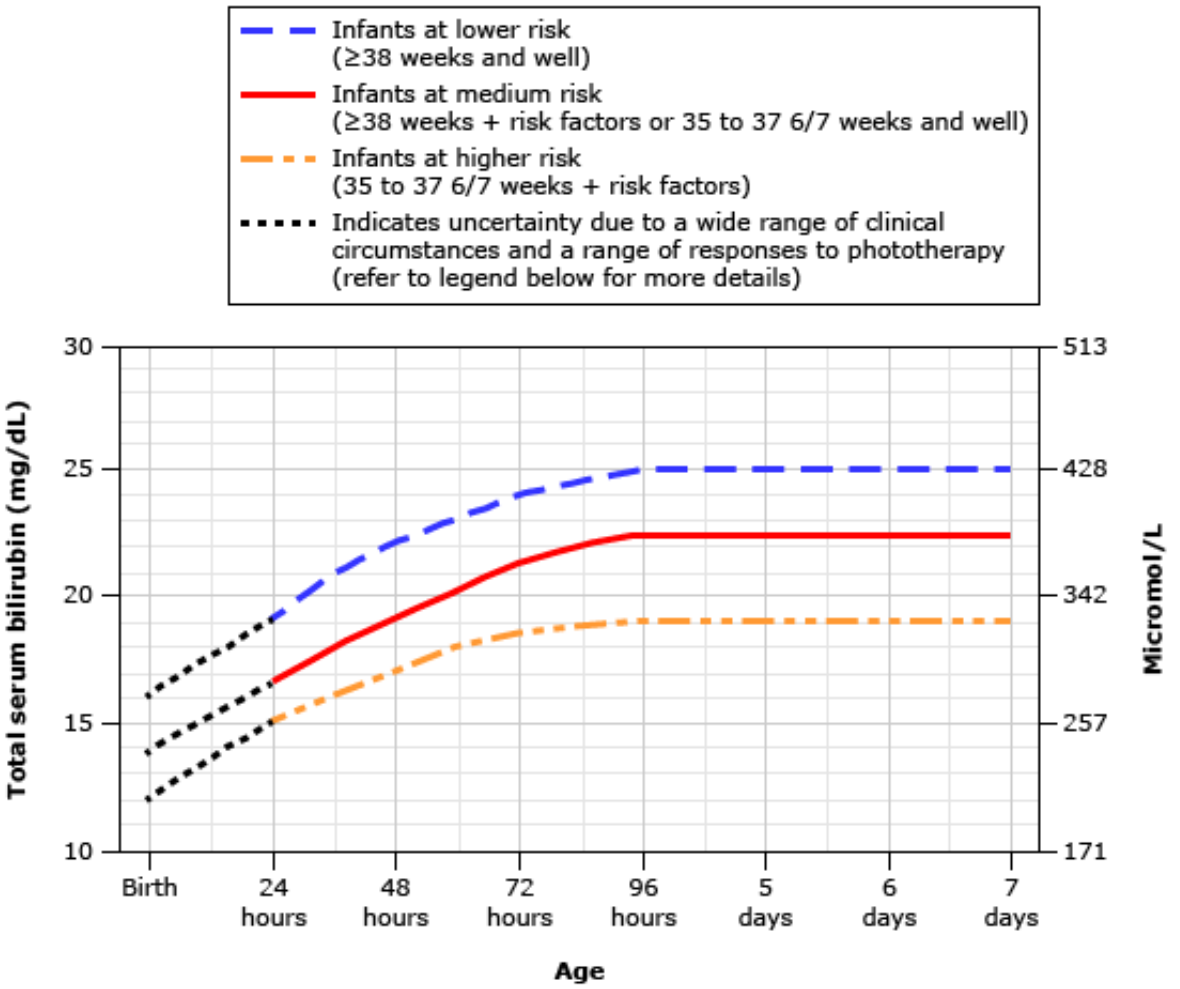
Δ Clinical assessment for risk factors for severe hyperbilirubinemia (TB >20 mg/dL [342 micromol/L]) entails documenting the presence of jaundice, evidence of hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), evidence of significant bruising (cephalohematoma), gestational age 35 to <37 weeks, previous sibling having received phototherapy, exclusive breastfeeding with excessive weight loss, and East Asian ethnicity.

◊ The risk for severe hyperbilirubinemia and the threshold for intervention (phototherapy and exchange transfusion) can be determined using the newborn hyperbilirubinemia assessment calculator based on TB and the presence of concomitant risk factors. The newborn hyperbilirubinemia assessment calculator provides information when the threshold has been reached for either

phototherapy or exchange transfusion. Risk categories for asymptomatic newborns include: term infants without risk factors, term infants with risk factors, late preterm infants without risk factors, and late preterm infants with risk factors.
§ Criteria for intervention are determined by TB and the presence of concomitant risk factors. Exchange transfusion is reserved for infants with signs of bilirubin-induced neurologic dysfunction (BIND) and when intensive phototherapy fails to prevent severe hyperbilirubinemia. The threshold for intervention is discussed in the UpToDate topic on the management of unconjugated hyperbilirubinemia in term and late preterm infants.

Graphic 126142 Version 1.0

Guidelines for exchange transfusion in infants 35 or more weeks gestation



The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy. Immediate exchange transfusion is recommended if the infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TB is ≥5 mg/dL (85 micromol/L) above these lines. Risk factors include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, and acidosis. Measure serum albumin and calculate B/A ratio. Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin. If infant is well and 35 to 37 6/7 weeks (medium risk) can individualize TB levels for exchange based on actual gestational age. Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the TB rises to these levels despite intensive phototherapy. For readmitted infants, if the TB level is above the exchange level, repeat TB measurement every two to three hours and consider exchange if the TB remains above the levels indicated after intensive phototherapy for six hours.

TB: total serum or plasma bilirubin; G6PD: glucose-6-phosphate dehydrogenase; B/A: bilirubin/albumin.

Graphic 68219 Version 23.0

Contributor Disclosures

Ronald J Wong, BA Nothing to disclose **Vinod K Bhutani, MD, FAAP** Nothing to disclose **Steven A Abrams, MD** Grant/Research/Clinical Trial Support: Fresenius Kabi [Parenteral nutrition-associated liver disease]. Consultant/Advisory Boards: MilkPep [Childhood nutrition]. **Melanie S Kim, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy